Remarks

The invention, as defined by pending claims 1, 2 and 5 to 20, provides dosage forms which show increased bioavailability of ophthalmologically active compounds by their provision in a dosage form of an ophthalmic treatment liquid which takes the form of a jet or stream of droplets. As explained below, Applicants respectfully submit that the claimed dosage forms are not obvious over the cited reference, EP 0 224 352.

Rejection Of Claims 1, 2 and 5 to 20 Under 35 §U.S.C. 103(a) Over EP 0 224 352

The Action has rejected claims 1, 2 and 5 to 20 as allegedly being obvious over EP 0 224 352. The Action alleges that the '352 reference differs from the claimed invention in droplet diameter and discharge velocity and that it allegedly would have been obvious for a person skilled in the art to use the teachings of this reference to arrive at the claimed invention. Further, the Action alleges that there is no evidence of record to demonstrate the advantage of the claimed dosage form over any other dosage form which has been administered in a droplet spray form. Applicants respectfully disagree.

Applicants have provided evidence of the greater bioavailability of the claimed dosage forms in the specification. In EXAMPLE 1, beginning at page 1, paragraph [0010] to page 2, paragraph [0021], the % increase in pupil diameter was compared after dosing white New Zealand rabbits with: I → 25 µl of 1% aqueous ephedrine hydrochloride solution (250 µg) via pipette (instillate); II → 5 µl of 5% aqueous ephedrine hydrochloride solution (250 µg) via pipette (instillate); and III → 5 µl of 5% aqueous ephedrine hydrochloride solution (250 µg) in a jet/stream of droplets of diameter in the range of 200 to 400 µm. As shown in Figure 1, the mydriatic response obtained from III, the 5 µl ocular droplet dosage form administered in a jet/stream of droplets, was more pronounced and was maintained over a longer duration compared to both instillates I and II.

In contrast, the '352 reference discloses a similar experiment in Example 1, beginning at page 6, line 30 to line 51, in which the % increase in pupil diameter was measured in white New Zealand rabbits following administration of a solution of ephedrine (350 µg), formulated as a 10% solution (3.5 µl) in a mixture of dimethyl isosorbide:water (9:1) which also contained hydroxypropyl cellulose (4% wt/wt), by an electrostatic spraying device. While this experiment demonstrates that there is a significant magnitude and duration of mydriatic response to the ephedrine formulation when applied at a considerably lower volume than conventional methods, it requires 1.4 times the amount of ephedrine (350 µg vs. 250 µg) compared to the claimed dosage forms to produce this effect.

Applicants have provided further evidence of the greater bioavailability of the claimed dosage forms in Example 2 of the specification. In EXAMPLE 2, beginning at page 2, paragraph [0022] to page 3, paragraph [0031], the % decrease in pupil diameter was compared after dosing white New Zealand rabbits with 30 µl of 1% aqueous pilocarpine hydrochloride solution (300 µg) instilled via pipette into the

conjunctiva sac with rabbits dosed with 5 µl of 1% aqueous pilocarpine hydrochloride solution (50 µg) applied as a jet and/or stream of droplets (with a diameter in the range of 200 µm to 400 µm) to the surface of the cornea. As shown in the table, there was no statistically significant difference in the calculated values of RRmax, Tmax or AUC between either of the treatments. Thus, this work demonstrates that an ophthalmic dosage form comprised of a jet and/or stream of droplets can produce an equivalent pharmacodynamic effect to a standard eye drop with only 1/6 of the drug.

In contrast, the '352 reference discloses a similar experiment in Example 2, beginning at page 6 line 53 to page 7, line 3, in which the % decrease in pupil diameter was measured in white New Zealand rabbits following administration of 3.5 µl of a 4 % w/w solution of pilocarpine (140 µg, assuming the density of the solution is 1 g/ml), in dimethylisosorbide:water (95:5 w/w) containing 3% hydroxypropyl cellulose as a viscolizer, by an electrostatic spraying device. While this experiment demonstrates that there is a significant magnitude and duration of miotic response to pilocarpine formulation when applied at a considerably lower volume than conventional methods, it requires almost 3 times the amount of pilocarpine (140 µg vs. 50 µg) compared to the claimed dosage forms to produce this effect.

As discussed above, the claimed dosage forms show an unexpected and significant increase in the bioavailability of ophthamologically active compounds compared to the electrostatic spray forms disclosed in the '352 reference. This reference does not teach or suggest any dosage forms having similar levels of bioavailability. Nor does this reference teach or suggest modifying the electrostatic spray device or spray forms thereof, to arrive at the instantly claimed dosage forms. Absent a teaching or suggestion in the prior art, one of skill in the art would not have been motivated to do what Applicants now claim. Thus, the claimed dosage forms are not obvious over the '325 reference. Applicants respectfully request reconsideration and removal of this objection.

A petition for a two month extension of time as set forth in 37 CFR §1.136(a) and the fee set in §1.17(a) for a non-small entity is included with this submission.

Respectfully submitted,

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